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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

JACQUES PARIS et al

Group Art Unit: 1614

Examiner:

Serial No. 10/753,073

Filed: January 8, 2004

For: CONTRACEPTIVE METHOD AND COMPOSITION

PETITION FOR ACCELERATED EXAMINATION

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In accordance with MPEP 708.02, Applicants request that the above-identified application be granted special status.

A. The fee for this Petition is paid by Credit Card Form (Form PTO-2038).

B. Applicants agree that in the event of a restriction requirement, an election will be made without traverse.

C. The present application is a continuation-in-part of prior Application Serial No. 09/284,147 filed May 17, 1999 and a continuation-in-part of Serial No. 09/423,108 filed June 12, 2001. Since the subject matter of this application corresponds substantially to the subject matter claimed in Serial No. 09/423,108, Applicants submit herewith the Search Report of the PCT application upon which 09/423,108 is based,

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and a copy of the list of references cited in the U.S. application.

D. A copy of a full translation of the Jamin reference, which was used to reject the claims in 09/423,108 is enclosed.

E. In 09/423,108, the claims were rejected under 35 USC 103 over Jamin. Jamin describes a contraceptive method using a high dose of progestogen alone which is outside of Applicants' range to be administered to women who have had contraindications to the standard estrogen-progestogen oral contraceptive, namely hypertension, thrombotic risks, hyperlipidemia, diabetes or benign breast disease. In the method of Jamin, the oral administration of nomegestrol acetate in the amount of 5 mg was needed to achieve contraception, and the contraceptive results were good. However, the use of this high dosage resulted in hypoestrogeny, and therefore, a poor bleeding pattern resulted. To combat this, Jamin proposed to separately administer percutaneously a low dose of estradiol. The added estrogen had nothing to do with the contraceptive effect, and its only role was for compensation of the hypoestrogeny induced by the high level of nomegestrol.

In contrast thereto, Applicants contraceptive method is directed to the use of oral compositions combining estradiol, an ester thereof, or equine conjugated estrogen and nomegestrol, the main role of the estradiol is to potentiate

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the anti-gonadotropic effect of nomegestrol and the hypoestrogenic compensation does not relate to the contraceptive effect.

Applicants' invention is thus directed to the unexpected and never before described potentiation of the anti-ovulatory activity of nomegestrol by estradiol, which permits women to use lower dosages of nomegestrol with the same efficacy and therefore with better safety. The dosages of nomegestrol are lower than those used by Jamin, which moreover, does not teach the oral administration of estradiol but rather a percutaneous administration of 50 μm of estradiol per day to compensate for the hypoestrogenic status induced by the high dosage of nomegestrol.

As Applicants have complied with the requirements of MPEP 708.2, accelerated examination of this application is requested.

Respectfully submitted,

Ira J. Schultz
Registration No. 28666

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RAPPORT DE RE' 'ERCHE INTERNATIONALE

nande Internationale No
PCT/FR 00/02952

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
C IB 7 A61K31/57 A61P5/30

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	FR 2 754 179 A (LABORATOIRE THERAMEX) 10 avril 1998 (1998-04-10) cité dans la demande revendications 1,2,4,8,9,13-15 page 5, ligne 6-14 _____	1-12, 14-17

☐ Voir la suite du cadre C pour la fin de la liste des documents

☒ Les documents de familles de brevets sont indiqués en annexe

° Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

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"Y" document particulièrement pertinent; l'inven tion revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

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Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
6 avril 2001	17/04/2001

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande Internationale No
PCT/FR 00/02952

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
FR 2754179 A	10-04-1998	AU 4627397 A	05-05-1998
		BR 9712274 A	31-08-1999
		CN 1239893 A	29-12-1999
		EP 0956022 A	17-11-1999
		WO 9815279 A	16-04-1998
		HU 9904508 A	28-06-2000
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		PL 332610 A	27-09-1999
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		TR 9900764 T	21-07-1999

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Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/423,108	PARIS ET AL.	
Examiner	Art Unit	Page 1 of 1
Sabiha N. Qazi	1616	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,500,814	12-2002	Hesch, Rolf-Dieter	514/170
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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INFORMATION DISCLOSURE CITATION IN AN APPLICATION

(Use several sheets if necessary)

OIPE JUN 03 2004 JC98 PATENT & TRADEMARK OFFICE

Sheet 1 of 1

Docket Number (Optional)	Application Number
GEI-074	09/423,108
Applicant J. PARIS et al	
Filing Date 10/29/99	**Group Art Unit** 1616

14

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

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FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation YES	Translation NO
SO2	2 754 179	4/98	France				X

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED
SABITA QAZI	7/17/03

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/423,108	PARIS ET AL.	
Examiner	Art Unit	Page 1 of 1
Sabiha Naim Qazi	1616	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A.	US-			
	B	US-			
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	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Jamin, C. (POPLINE database, abstract of Revue Francaise De Gynecologie Et D Obsterique, 1992, 87(6): 370-6)
	V	
	W	
	X	

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Progestational contraception: Advantages

C. Jamin*

Progestational contraceptive: advantages

In spite of the nearly total effectiveness of classic estrogen-progestogen oral contraception and its good overall tolerance, in a not considerable number of situations, yet it is not possible to resort to it. These situations are the following: high blood pressure, hyperlipemia, diabetes, minor mastopathy, pre-menstrual tension either spontaneous or under estroprogestogen therapy. Macroprogestational contraception using either pregnanes (chlormadinone acetate) or norpregnanes, promegestone, nomegestrol acetate, can be then the right solution. Clinical and metabolic tolerance is excellent. In the occurrence of hypoestrogenism symptoms, a combination of nomegestrol acetate-estradiol 17 ß transdermally administered, has given top results in a preliminary study.
(Contrcept.Fertil.Sex., 1932, 32.2.123-128.)

Key words: Progestational contraception – Metabolism – Nomegestrol acetate- Transdermal estradiol.

The efficacy and tolerance of combined oral contraceptives in women under 40 is now such that future progress will be slow and difficult to achieve and quantify.

Efficacy is virtually complete provided that compliance is good. An improvement in compliance is however possible and can take many forms, from long-lasting contraception to emergency contraception.

Long-term tolerance is also good on the whole. The risk of atheroma is probably not increased by the pill and may even be decreased. The risk of cancer of the ovary, endometrium and even maybe the pancreas is lower. As for breast cancer, studies to date are reassuring. In this last area, progress is needed, but will depend on greater understanding of breast cancerogenesis. There are still problems controlling the cycle in some women at the start of treatment, due to swollen breasts, headaches, etc.

However, there are subgroups of women, where considerable improvement is still possible. Some subgroups are easy to identify – those with hypertension, diabetes or hyperlipidemia, while some are impossible to identify – women at risk of thrombo-embolism.

Although conventional combined contraception is generally well tolerated in young women, improvement is desirable at the individual level, so that oral contraception can be offered to women in whom estroprogestins are poorly tolerated or contra-indicated.

In women over 40, the situation is much more complicated, in particular in smokers. However, effective contraception is more important than ever at this time of life.

The frequency of individual risks, metabolic in particular, increases with age and additional difficulties related to tissue anomalies such as fibroma, endometrial hyperplasia and mastopathy complicate the situation.

However, in addition to contraception, use of the pill at this age would help maintain a satisfactory hormone balance until the menopause and the start of hormone replacement therapy. Conventional contraception with synthetic estroprogestins could be an ideal solution.

Paper received at the editorial office 11th November 1992
Accepted 1st December 1992
Presentation made at the 20th Conference on Fertility and Orthogenics 7th, 8th, 9th November 1992 at the Palais des Congrès, Paris
Contracept. Fertil. Sex.-1993- Vol.21n°2.pp.123-128

Hormone balance is stable, particularly since the antigonadotropic effect inhibits the natural variations related to the perimenopause. Women could enjoy effective contraception, avoid hot flushes, perimenopausal bone loss, premenstrual syndrome, hyperplasia of the endometrium, menorrhagia, mastodynia, with the subsequent risk of cancer of the endometrium, character disorders, etc.

Three prospective studies have tempered the enthusiasm generated by the idealistic picture above (7), the study by the Royal College of General Practitioners "RCGP", that by the Oxford Family Planning Association and the Walnut Creek Contraceptive Drug Study. These three trials revealed a marked increase in cardiovascular risk, myocardial infarction, cerebrovascular accidents, venous thrombotic accidents and hypertension. The risks were much higher in smokers. In a later study published in 1981, the RCGP only found an increased risk in smokers. The marked improvement in the results was attributed to the decrease in doses of ethinylestradiol and progestins in the pills and to elimination of high-risk patients. The first studies prohibited prescription of OP in diabetic, hypertensive, obese and hyperlipidemic women and those with a history of thrombo-embolism, smokers, and espcially women over 40.
Later work by Porter, in particular covering the years 1980 to 1982 only showed an increase in the thrombo-embolic risk RR = 2.8. Neither Porter nor Mitchell found an increase in mortality in women taking oral contraceptives at the dosages then used (≤ 50 µg ethinylestradiol).
It is probable that the reduced risk is attributable to the association of a better selection of patients receiving the pill with a decrease in ethinylestradiol doses. The introduction of less androgenic progestins was still at this time theoretical and could not influence interpretation of the clinical studies.

Based on this data, is it possible to propose an extension in the use of progestins? It is clear that the age of 38 or 40 should no longer be considered a cut-off point, but currently no studies are available suggesting that synthetic OP could be used in smokers or women with one of the listed cardiovascular risk factors.
The questions related to modification in risk factors under oral contraception referred to above have still not been resolved. Although there is generally a reduction in LDL cholesterol and an increase in HDL cholesterol with the new generation of OP, in a number of women hypercholesterolemia involving LDL occurs on the pill, whatever the pill and whatever the dose.

The adverse effects on the glucose balance are also considerably reduced by use of very low doses of EE2 and only slightly androgenic progestins but some anomalies persist.

However, today, it is admitted that the risk is not atherogenesis but hypertension and thrombo-embolism. In subjects predisposed to hypertension, EE_2 would appear to have an effect on the liver producing an increase in angiotensinogen. Reducing the EE_2 content from 50 to 30 or 20 µg does not appear to have a radical effect on this problem.

The main question is whether the new pills are devoid of effect on coagulation.

A decrease in the dose of estrogens from 50 to 30 µg seems to be accompanied by a 50% decrease in the risk of venous thrombosis and pulmonary embolism. However, the relative risk (RR) of venous thrombosis in the group taking oral contraception was still about 1.5 times higher (11). The risk of arterial thrombosis is poorly evaluated and the role of the progestin may be real. It was hoped that a decrease in the dose of estrogens and use of less androgenic progestins would lead to an improvement in the coagulation factor profile. Although a slight improvement was noted, anomalies persist (increase in fibrinogen, fibrinopeptide A and fragment E, reduction in fibrinolytic activity and antithrombin III). The sole difference seems to be that only the 50 µg pill increases deposits of fibrin ex vivo on rabbit aorta sub-endothelium in the presence of blood from women treated with OP. Desogestrel appears to stimulate synthesis of prostaglandins while norgestrel and desonorgestrel are apparently devoid of this effect (8). The increase in Pgl2 would have a favorable role in locally decreasing platelet aggregation and increasing vascular flow.
Whereas there is no real problem related to atherogenesis on these pills, women at risk of diabetes, hypertension and hypercholesterolemia should not use this contraceptive method. The thrombo-embolic risk is dose-dependent with estrogen and persists at a lower level in low estrogen pills. The risk of arterial thrombosis, which is major in the presence of other risk factors such as smoking, hypertension and atherogenic hyperlipemia, is probably increased even with the so-called modern preparations.
It remains to be seen whether age is an independent risk and, if so, which age.

PROGESTIN ONLY CONTRACEPTION

We will only cite contraception involving injectable progestins and microprogestins here. Control of the cycle and ovarian function are unsatisfactory in particular in perimenopausal women.

There are no licenses in France for high-dose progestins but use is nevertheless widespread. In general, used 20/28 days it mostly involves two types of compound: testosterone derivatives (19 nor) and progesterone derivatives (17 OH and 19 nor).

The theoretical justifications for use of high-dose progestin contraception

There are two main reasons for using this form of contraception:

- the anti-estrogen effect
- the need to avoid metabolic anomalies.

The anti-estrogen effect

This effect may be desirable at all ages, but it is after 40 that absolute or relative hyperestrogenemia is most common. This has been attributed to anomalies in perimenopausal ovulation, but even if there are no clinical or laboratory signs of excess estradiol secretion and / or progesterone insufficiency, a number of women present estrogen receptor disorders involving intolerance to estradiol, in particular affecting the breasts or uterus.

An anti-estrogen effect is desirable:

- in premenstrual syndrome with sensation of swelling, mastodynia, nervousness and weight gain
- in menstrual disorders: menorrhagia due to hyperplasia of the endometrium is particularly sensitive to this type of treatment.
- In benign mastopathy, including fibro-adenoma and fibrocystic diseases of the breast. The anti-estrogen activity is clinically clear, provided that treatment is started early in the cycle, which is the case with contraception.

In the prevention of cell pathologies which are common after 40: hyperplasia of the endometrium, fibro-adenoma of the breast, cancer of the endometrium.

Some authors even consider that there may be a preventive effect in uterine fibroma, endometrial polyps and breast cancer.

Origin of anti-estrogen activity

Progesterone increases transformation of estradiol into estrone by stimulating 11ß OH steroid dehydrogenase. It increases sulfation of estrogens and decreases estradiol cell receptors. These properties have been demonstrated in the endometrium and breast (9, 10). Some progestins have considerable antigonadotropic activity. This is the principal means of observing the desired effect on the breast. This property seems to require that treatment be started before ovulation. Finally, the anti-estrogen effect of 19 nortestosterone derivatives is probably increased due to their androgenic properties. However, for some of them, in situ aromatization has been suggested, which would lead to a loss of some of the anti-estrogen properties.

Metabolic aspects of progestin only contraception

Whatever the dose and compound, the conventional combined contraceptive pill is still associated with metabolic, blood pressure and coagulation anomalies. These products are therefore contra-indicated in at-risk women and probably after a certain age, which varies depending on the patient.

Testosterone derivatives (19 nortestosterone) were the first to be used and still have their supporters today because of the good control of the cycle, the antigonadotropic activity and the potency of the anti-estrogen effect (14).However metabolic problems and signs of hyperandrogenia are not unusual so that other compounds are needed especially in women at risk of vascular effects. This form of contraception can only be used in specific indications.

Progesterone derivatives (17 OH progesterone and 19 norprogesterone) were studied in healthy subjects and subjects at risk (Table 1).

Table 1: Metabolic effects of progestin contraception

Progestin and Ref.	Weight	Pa	S. renin	AT III	CT	TG	HDLC	LDLC	Apo ß	Apo A1	Gty	Insul.
Ac. Chlorm. 10 mg/d n = 20, d = 6c Pelissier, 1987	=	=	=	=	=	=	=	=	=	Dec	=	=
Promogest. 1 mg/d n = 17, d = 4c Basdevant, 1989	=	=	=	=	=	=	=	=	=	=	Dec	=
Ac. Nomeg, 5mg/d n=36, d= 6c Basdevant, 1991	=	=	=	Inc	=	=	=	=	=	Dec	=	=

Chlormadinone acetate (Luteran ®) was used at a dosage of 10 mg in two daily doses in women at high risk of vascular disease. Twenty women were followed for 6 months and 92 women for a variable time (totalizing 1559 months?) (16, 17).
Weight remained stable. There were no significant variations in blood pressure or the renin substrate. From a metabolic viewpoint, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and apo B were not affected but there was a significant decrease in apoprotein A1. Blood insulin and glucose levels did not change nor did the antithrombin III or protein C levels (16).
The promegestone Surgestone was studied at double the usual dose (1 mg) commonly given in contraception (0.5 mg/day) in 17 patients during 4 cycles. These patients were suffering from fibrocystic disease of the breast. The systolic and diastolic blood pressure did not vary significantly during the study, nor did the angiotensinogen level. Weight and blood insulin did not change significantly. Blood glucose levels fell ($p<0.05$), while the insulin level remained stable. Total cholesterol, HDLC, LDLC, triglycerides, apo A1, apo B and antithrombin III did not vary significantly. This study was performed in a small number of metabolically healthy subjects over a short time. According to the author, the results cannot be extrapolated to at-risk patients or long-term administration and the statistical study should be confirmed in a larger population (2).
Nomegestrol acetate (Lutenyl ®) was given at a dose of 5 mg (1 tablet daily) to 36 healthy women for 6 months. Weight remained stable as did the following parameters: cholesterol, triglycerides, HDLC, LDLC, apo B, glycemia, insulinemia, plasminogen, fibrinogen and angiotensinogen. There was a small reduction in apo A1 and a slight increase in antithrombin III (1). The blood pressure remained stable as measured manually.
The three compounds examined were neutral from the metabolic viewpoint. The only changes observed (reduction in apo A1 and increase in antithrombin III in particular) were probably attributable to the mean reduction in estradiol levels and have no adverse influence. These modifications were found with all 3 products and the difference in significance seems to be a statistical artifact related to differences in the sample size, duration of treatment and standard deviations.

Mechanism of contraceptive effect

Few studies have been performed on the mechanism of the contraceptive effect of chlormadinone acetate (AC). It seems that, in the group published, a number of women had anovulatory cycles. A drop in estradiol and LH levels with no change in FSH and a disappearance of progesterone levels were noted. This suggests inhibition of ovulation due to an antigonatodropic effect (16, 17).

A study on promegestone (PMG) in 6 women with regular cycles showed absence of ovulation measured by progesterone levels and disappearance of the LH peak (5). In another study, the antigonadotropic activity was detected but at a lower level than that measured under lynestrenol (18).
The contraceptive effect of nomegestrol acetate (NA) has been studied particularly thoroughly. This substance inhibits ovulation with disappearance of progesterone secretion and a reduction in the LH level and disappearance of the peak (3). As regards the vaginal mucus, in a very impressive study, Chrétien (6) demonstrated changes in the mucus rendering it hostile to spermatozoa. Finally, there seems to be a direct effect on the ovary with this compound involving inhibition of estrogen production by follicles recruited during the previous cycle (4).

Disadvantages of the method

The first disadvantage is that these substances have no marketing authorisation in this indication and that there is no Pearl index.
From a practical point of view, the incidence of menstrual disorders is not clearly determined (Table 2).

Table 2 Frequency of cycle disorders

Ac. chlor	n=92 d=6c	menorrhagia amenorrhagia	n=25 n=15
PMG	n=6 d=2c	Troubles= 30% (?)	
Ac. Nom	n=36 d=6c	spotting amenorrhagia	n=16 n=1

With AC, in 92 women there were 25 cases of metrorrhagia and 15 cases of amenorrhea (17).
With promegestone (PMG), figures are only available for a short time (2 months) and in very small series (6 women) at a dose of 0.5 mg. It is just stated that there were 30% of menstrual disorders with no further details (5).

With NA, in a study on 36 women followed for 6 months, 17 women presented a disorder with the cycle, 16 cases of spotting and 1 of amenorrhea (1).

Hypo-estrogenemia is often the desired effect in women with a gynecological problem, although this is not so when this type of contraception is used in women with metabolic anomalies or healthy women over 40 (Table 3). Sufficient estrogen levels are required to avoid premature bone loss and for many other reasons, particularly metabolic reasons (enhanced clearing of LDL and production of HDL). In young women, normal blood estradiol levels are highly desirable to achieve a satisfactory bone mass peak.

Table 3: Blood estradiol levels (between D16 and D25) with promegestone, chlormadinone acetate and nomegestrol acetate 20 days/month

	Number of subjects	Duration (months)	E_2 tpg/ml	References
Ac. Chlorm	20	3	45 ± 9	Pelissier, 1987
(10mg/24h)		6	55 ± 12	Pelissier, 1991
		12	34 ± 23	
PMG	6	2	30.8 ± 23	Blacker, 1986
(0.5 mg/24h)	2	2	35 ± 3	V D Linden, 1985
Ac. Nom	36	3	39.8 ± 10	Basdevant, 1991
(5 mg/24 h)		6	27.6 ± 3.5	

Table 4: Plasma estradiol in pg/ml during the 2nd cycle of treatment with promegestone 0.500 mg/day from D6 to D25 in 6 women

8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
100	50	30	10	25	20	25	30	10	10	30	10	10	10	20	10	25	10
85	40	50	50	10	30	25	10	10	10	10	10	40	40	10	30	30	10
128	77	80	145	88	34	65	15	38	39	33	55	45	60	55	40	10	50
125	120	140	45	65	30	10	20	20	10	60	10	45	60	10	25	30	10
90	105	80	130	100	75	30	20	25	30	30	40	30	40	70	50	40	35
118	130	120	155	80	95	55	65	50	45	70	80	90	47	62	97	100	70

The use of conventional contraceptives was contra-indicated for most of these women: hypercholesterolemia on the conventional pill, 14/18 cases; benign mastopathy, 4/18 cases and diabetes 1/18 cases.

The duration of administration is currently 3 months for the most recent inclusions and 3 years for the oldest ones (Table 5).

To date efficacy is perfect. No pregnancies have occurred. Menstruation is regular in all cases and clinical tolerance excellent. The blood pressure and weight are stable and, as regards lipids, no women have yet shown hypercholesterolemia, which was responsible for withdrawal of the conventional pill. Lipid fraction and apoprotein levels are unchanged from the baseline values.

The association of cyproterone acetate and transdermal estradiol has already been used but seems less maniable from the clinical and biological points of view leading to less regular withdrawal bleeding (12) and minimal metabolic variations (13). This product cannot therefore be used as a contraceptive except in specific indications.

With AC, the levels at 3 months were 45 ± 9 pg/ml (15-105); at 6 months 55 ± 12 (15-200), n = 20 (sampling time in the cycle variable (16)); at 12 months 34 ± 23 pg/ml, n=11 and at 30 months, 50 ± 36 pg/ml (15).

With PMG (5) in 6 women at 12 months on D20, E2=30.8 ± 25 pg/ml (10-70), the estradiol blood level fell on D8 and then remained stable (Table 4). Another study found equivalent figures with E2 = 35 ± 3 pg/ml (18).

With NA in 36 women at 3 months, E2 = 39.8 ± 10 pg/ml and at 6 months, 26.7 ± 3.5 pg/ml (1).

The reduction in estradiol levels varied with the same product from one woman to another in intensity and kinetics. It is not stated whether this was due to variability in individual sensitivity and/or to variations in the interindividual pharmacokinetics of the substance. The available figures suggest that there is no difference between the products.

Table 5: Contraception with nomegestrol acetate + 0.05 mg transdermal estradiol.
n = 18, duration 3 to 36 cycles, m=16, total = 272 cycles

Indication

- Hypercholesterolemia n = 14
- Mastopathy n = 4
- Diabetes n= 1

Regimen

- Start on day 1 of cycle for 20/28 days
- 5 mg nomegestrol acetate + 1 TTS 50 changed twice weekly

Results

- Stable weight, regular cycles
- CT, TG, apo B, apo A1, blood glucose stable

Pregnancy = 0

A NEW CONTRACEPTIVE

In a preliminary study, we examined the contraceptive efficacy of an association of 5 mg/day nomegestrol (Lutenyl ®) and estradiol given by the transdermal route (Estraderm TTS 50 changed twice a week) in 18 women aged between 19 and 40. These women had cycle disorders under progestational contraception and both products were given for 20/28 days starting on day 1 of the cycle.

This preliminary work is encouraging. The improved clinical and biological tolerance of progestin-only contraception and conventional oral contraception gives women an alternative if the usual oral contraception is contra-indicated for mammary or metabolic reasons, and in women over 40. It is obviously necessary to confirm these results in a controlled study in a larger population.

Despite the progress made in doses and substances used in combination pills, to date these still cannot be prescribed to women with a high cardiovascular risk based on metabolic risk markers and epidemiological studies.

In addition, in the over forties, the battle against hyperestrogen levels may be added to the other risk factors. Progestin contraception gives excellent results from a metabolic viewpoint and reduces the clinical signs of hyperestrogenemia. However, the three products used in this indication sometimes give minor cycle anomalies and insufficient blood estradiol levels. In these cases, addition of transdermal 17 ß estradiol to nomegestrol acetate maintains contraceptive activity, improves control of the cycle and does not affect metabolic tolerance.

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I the undersigned, Expert Translator for the Court of Appeal of Aix-en-Provence, certify that the above translation is true to the original written in French.

Sophia Antipolis, 30 May 2003

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